Synthesis and SAR of b-Annulated 1,4-Dihydropyridines Define Cardiomyogenic Compounds as Novel Inhibitors of TGFbeta Signaling.

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Public Summary:
We used high throughput screening of chemical library to discover small drug-like molecules that promote progenitor cell to cardiomyocyte differentiation. One active compound is described in this paper. The molecule, named ITD-1, is the first selective inhibitor of Transforming Growth Factor-beta signaling. Other inhibitors of TGF-beta act by blocking the catalytic activity of its cell surface receptor, and do not distinguish between it and closely related receptors. ITD-1, in contrast, selectively causes the type II TGF-beta receptor (TGFBR2) for internalization and degradation. Inhibition of TGF-beta constitutes a critical step necessary for the differentiation of uncommitted progenitor cells into cardiomyocytes. Furthermore, ITD-1 might be developed further into an drug for blocking TGF-beta function in vivo in a number of clinical settings.

Scientific Abstract:
A medium-throughput murine embryonic stem cell (mESC)-based high-content screening of 17000 small molecules for cardiogenesis led to the identification of a b-annulated 1,4-dihydropyridine (1,4-DHP) that inhibited transforming growth factor beta (TGFbeta)/Smad signaling by clearing the type II TGFbeta receptor from the cell surface. Because this is an unprecedented mechanism of action, we explored the series' structure-activity relationship (SAR) based on TGFbeta inhibition, and evaluated SAR aspects for cell-surface clearance of TGFbeta receptor II (TGFBR2) and for biological activity in mESCs. We determined a pharmacophore and generated 1,4-DHPs with IC(50)s for TGFbeta inhibition in the nanomolar range (e.g., compound 28, 170 nM). Stereochemical consequences of a chiral center at the 4-position was evaluated, revealing 10- to 15-fold more potent TGFbeta inhibition for the (+)- than the (-) enantiomer. This stereopreference was not observed for the low level inhibition against Activin A signaling and was reversed for effects on calcium handling in HL-1 cells.